Reviewer's report

Title: Short-term physiological effects of nicotine-free e-cigarette compared to regular cigarette in smokers and non-smokers: a randomized trial

Version: 2 Date: 18 February 2015

Reviewer: Francesco Pistelli

Reviewer's report:

General comments
This is a clinical study aiming to assess, in current smokers as compared to non-smokers, the effects of the short-term (5 minutes) use of both a nicotine-free electronic cigarette (NFe-cig) and traditional tobacco cigarette, on measurements of lung function (forced expirograms), and fractional concentration (Fe) of carbon monoxide (CO) and nitric oxide (NO) in expired air.

A convenient small sample of subjects (n = 10 smokers and n = 10 non-smokers) was analyzed, by using standardized protocols and applying adequate methods of laboratory testing.

Main conclusion is that the use of the study NFe-cig does not have acute effects on measurements of lung function, FeCO and FeNO in non-smokers, and a small effect on FEV1 and FEF25 in smokers.

Major compulsory revisions

1. The reason for which it was chosen that specific NFe-cig for this study should be clearly stated. There are tens of different electronic cigarettes currently available on the market. Throughout the manuscript, it should be specified that the observed results are related to that specific NFe-cig evaluated in this study, and cannot be generalized. For example: Discussion, page 9, line 180 “In this study we have demonstrated that the use of NF e-cigarettes was not associated with major acute physiological changes”; Conclusions, page 12, line 271 “In conclusions in this randomized trial we have shown that the use NF e-cigarettes was found to have no immediate adverse physiologic effects after short-term use”.

2. The effects assessed in the present study are not all “physiological”. For example, it is not “physiological” for a non-smoker being exposed to high levels of CO. Moreover, this is not a “randomized trial”. Randomization was correctly applied when testing subjects. However, the study subjects are a convenient sample selected among local health personnel (“pulmonary fellows or attending physicians”, page 4 line 50). The terms “physiological effects” and “randomized trial” should be modified in the title and throughout the manuscript, including the keywords.

3. The study was conducted on a very small sample of subjects. This is an important limit of the study and should be adequately discussed, also in terms of
statistical analyses and obtained significant results.

4. There are evidences that electronic cigarettes may cause adverse effects such as cough, throat irritation, nausea etc. In the present study there is no mention of the possible subjective symptoms that the study subjects may have experienced. It should be noted that non(never)-smokers were enrolled in the study, that is subjects that potentially could have important acute symptoms when exposed to acute active electronic/tobacco smoking for the first time. This limit of the study should be clearly discussed.

5. The authors seem to attribute the adverse effects of the “electronic cigarettes” to their content in nicotine (see Discussion, page 9, lines 196-199). However, this is a speculative statement, since (at least to the best knowledge of this reviewer) there is no evidence with regard to this issue. Studies supporting this affirmation should be quoted otherwise this part of the discussion should be modified or eliminated.

6. The authors seem to attribute the decrease in FEV1 and FEF25, observed in smokers when using the NFe-cig, to some component different from nicotine (see Discussion page 11, lines 246-252). Also in this case, studies supporting this affirmation should be quoted. Moreover, the higher levels of FeCO observed in smokers, as compared to non-smokers, may be explained by the previous CO exposure from tobacco smoking in the formers. Indeed, according to study protocol, smokers should refrain from smoking in the 6 hours preceding the experimental testing while the half-life of expired CO is about 4 hours, depending on exercise.

7. Discussion, page 10, lines 220-225. It is not immediately clear to this reviewer how a “repetitive acute smoke effects may cumulate and ultimately lead to irreversible damage”. Possible long-term effects due to “electronic smoking” should be assessed in specifically designed studies and cannot be foreseen on the basis of the short-term effects observed in the present study, based on a single exposure of 5 minutes.

8. Methods, page 4, line 63. “All subjects were asked to use a similar pattern and frequency of smoke aspiration”. This is a very surprising instruction for the study protocol, since it seems difficult that a non-smoker may smoke a tobacco cigarette for 5 minutes, probably for his/her first time, as a regular smoker.

Minor essential revisions

9. Replace “pack/year” with “pack-years” throughout the manuscript

10. Results, page 8 lines 154 and 156. Replace “no smoker subjects” / “no smokers” with “non smokers”

11. Discussion, page 9, line 187 “Among the other measures to prevent tobacco smoking and to quit smoking”. According to the current available scientific evidences and guidelines for smoking cessation, the electronic cigarettes are not a preventive or treatment measure for tobacco smoking.

12. Discussion, page 9, line 199. Correct the misprint “of the of the”.


13. Discussion, page 11, line 237. Replace “that in smokers” with “than in smokers”.
14. Discussion, page 11, line 238. Replace “have induce” with “have induced”.
15. Discussion, page 11, line 240. Replace “that reported” with “than that reported”.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests